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BRIEF COMMUNICATION

Cognitive reserve and neuropsychological functioning in patients infected with hepatitis C

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Abstract

This study evaluated the influence of cognitive reserve on neuropsychological test performance in 198 patients infected with the hepatitis C virus. IQ scores, educational level, and occupational rating were combined to calculate a Cognitive Reserve Score (CRS) for each patient. Similar to studies of infection with the human immunodeficiency virus, there was a significantly increased risk of impairment in neuropsychological test performance in individuals with lower CRSs. It is important to account for CRS when assessing cognitive findings in large-scale clinical trials. (*JINS*, 2007, *13*, 687–692.)

Keywords: Liver diseases, Hepatic insufficiency, Intelligence, IQ, Cognitive manifestations, Neurobehavioral manifestations

INTRODUCTION

Interindividual differences in risk for disease or dysfunction are a well-recognized factor in clinical medicine. However, medical research has yet to routinely incorporate the concept of cognitive reserve (CR; Satz, 1993; Stern, 2003) in understanding how the brain accommodates, copes, and changes in the presence of pathology. Broadly defined, cognitive reserve refers to the discrepancy between the degree of pathology and the degree of functional impairment evidenced across individuals with the same disorder. The construct of CR has been posited as a potential explanation for individual susceptibility to disease states such as Alzheimer's disease and the variable levels of disruption in functional performance (Alexander et al., 1997; Wilson et al., 2004).

Proxy measures of CR generally include demographic variables such as levels of education and occupation and intelligence (IQ), viewed as reflecting the positive correlations among multiple cognitive measures (Humphreys, 1979), which sample the intellectual behavior repertoire of the individual (Humphreys, 1976–1977). As such, the variables of education and IQ have been proposed more as risk factors than as confounders (Satz et al., 1993) when studying the effects of disease state or treatment on cognition. In general, individuals with higher IQ are expected to perform better than those with lower IQ on cognitive tests. This

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finding has been demonstrated for measures as broad as the Halstead–Reitan Neuropsychological Test Battery (Warner et al., 1987) and as narrow as the Mini-Mental State Examination (Bieliauskas et al., 2000). Lezak (1988) has challenged the notion of IQ as a general measure, suggesting that it obscures many facts of a subject's neuropsychological status. However, earlier factor analytic work by Humphreys (1962) clearly describes how human abilities can be classified in a hierarchical manner, ranging from narrow and specific facets of abilities to a more general overarching factor. Indeed, measures of IQ seem to account for a significant portion of the variance in neuropsychological test performance, even more so than education variables (Steinberg & Bieliauskas, 2005). Nevertheless, Dodrill (1997) cautions that above-average general intellectual abilities may not always lead to above-average performance on cognitive tests, even though below-average intellectual scores are reflected in lower cognitive test performance.

An alternative method for estimating CR has been reported by Stern et al. (1996), which derives a Cognitive Reserve Score (CRS) by summation of the rank values of an individual's educational level, occupational category, and Shipley Institute of Living Scale vocabulary subtest *t* score. They found that human immunodeficiency virus-1 (HIV-1)–seropositive subjects with low CRSs exhibited significantly greater cognitive deficits than did HIV-1–seropositive subjects with high CRSs. This finding is similar to the earlier report of Satz et al. (1993), which suggested that low education might reflect lower CR that resulted in a lower threshold for neuropsychological abnormalities in cases of early HIV-1 infection.

It is therefore crucial to account for the influence of CR on cognitive variables in clinical trials as distinguished from the impact of various disease processes and/or their treatments. Even within a normal college student population, there is at least some base rate (15%) of "impaired" performance on a standard neuropsychological test battery (Axelrod & Wall, 2003). It is necessary to guard against attributing "impaired" test performance to a disease state or treatment status when, instead, poor performance may reflect naturally occurring variability. On the other hand, it is also possible that individuals with lower CR may be more susceptible to disease state or treatment status than individuals with higher CR.

We have previously reported that 33% of patients entering the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial with long-term pegylated interferon had evidence of a mild, nonfocal subcortical processing deficit, which was highly correlated with IQ, education, and occupation. We also demonstrated that IQ and depression (Beck Depression Inventory II, BDI) scores were significant and independent predictors of cognitive impairment (Fontana et al., 2005). The present study was designed to more closely analyze the relationship between measures of CR and the presence of cognitive impairment in hepatitis C virus (HCV) patients with advanced fibrosis involved in this clinical trial.

METHODS

Patient Population

The HALT-C Trial is being conducted at 10 clinical centers in the United States. Data collection and analyses are performed by a central data coordinating center (New England Research Institutes, Watertown, MA). Inclusion criteria for the main HALT-C Trial include a positive test for hepatitis C antibody (anti-HCV) and detectable HCV RNA in the serum, a liver biopsy performed within 12 months of enrollment demonstrating bridging fibrosis or cirrhosis (Ishak fibrosis score of 3 to 6), and evidence of nonresponse to prior treatment with at least 12 weeks of interferon α therapy that was completed more than 3 months before enrollment (Lee et al., 2004). Patients with any other coexistent liver disorder, a Child–Turcotte–Pugh score > 6, or a history of variceal hemorrhage, ascites, or hepatic encephalopathy were excluded. Additional exclusion criteria included intolerance to interferon, reactivity to anti-HIV, active use of illicit injection drugs, ongoing excessive alcohol consumption, a suicide attempt or hospitalization for depression within the past 5 years, a test for HIV that was positive within the previous 12 months, and a history of an uncontrolled psychiatric condition within the past 6 months such as severe depression, schizophrenia, or bipolar illness. All subjects entering the HALT-C Trial signed a written informed consent document. Participants in this ancillary study at the University of Michigan and University of Southern California also signed a separate institutional review board–approved consent form that highlighted the risks and benefits of cognitive testing at study entry and months 6, 12, 24, 36, and 48. In our prior study (Fontana et al., 2005), neuropsychological pretreatment scores of 201 HALT-C patients were analyzed.

Neuropsychological Tests

Patients underwent a battery of 10 demographically corrected neuropsychological tests on entry into the study (Fontana et al., 2005). The technicians administering the tests as well as the neuropsychologists scoring the tests were blinded to clinical data except for subject age, gender, and educational level as needed to calculate standard scores. Descriptions and references for all the tests as well as for score calculations and derivations of educational and occupational categories can be found in our earlier reports (Bieliauskas et al., 2006; Fontana et al., 2005). Tests were grouped by the following cognitive domains:

General Intellect: The Shipley Institute of Living Scale (Shipley) IQ scores, vocabulary subtest *t* scores, and abstraction subtest *t* scores.

Verbal memory: The Selective Reminding Test (SR).

Nonverbal memory: The Continuous Visual Memory Test (CVMT).

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Speed and efficiency of information processing: Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised, the Serial Digit Learning Test (SDLT) and Simple and Choice Reaction time.

Visuomotor tracking: The Trail-Making Test, Parts A and B, and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised.

Motor Skills: The Finger Tapping Test.

Executive function: The Wisconsin Card Sorting Test and the Controlled Oral Word Association Test.

Beck Depression Inventory II

Cognitive Reserve Score (CRS): This score was calculated according to the method of Stern et al. (1996). The score was derived from total years of formal educational, occupational category determined by the method of Barona et al. (1984), and vocabulary *t* score on the Shipley. The rank values of each of these three measures were summed to calculate the CRS.

Global Deficit Score (GDS): The GDS is a means by which standard scores can be summed from a battery of tests into a single global score. This method assumes that all standard scores have equal weighting. This method also helps account for patients with severe impairment in only 1 or 2 tests as compared with patients with mild impairments on multiple tests. A GDS was calculated, by averaging the deficit scores for standard scores (SS) for each subtest other than the Shipley on the following basis (Heaton et al., 1994):

Mean SS = 40+	DS = 0
Mean SS = 35–39	DS = 1
Mean SS = 30–34	DS = 2
Mean SS = 25–29	DS = 3
Mean SS = 20–24	DS = 4
Mean SS = <20	DS = 5

In our study, a GDS ≥ 1.0 was used to define the presence of cognitive impairment.

RESULTS

Originally, there were 201 subjects in this cohort; 3 were removed for the purposes of this study due to data missing for the calculation of the CRS. The Shipley IQ scores were normally distributed and similar to that of the general U.S. population ($M = 99.6$; $SD = 12.6$). Thus, there appeared to be no unusual skewing of general intellectual abilities in this sample.

Sixty-three patients (32%) were classified as cognitively impaired based on a GDS of 1 or greater. Patients who were classified as impaired had significantly lower IQ scores ($M = 91.0$; $SD = 12.0$) than patients classified as not impaired ($M = 104.0$; $SD = 11.0$), had a significantly lower level of education (see Table 1), and a lower occupational rating. Patients who were classified as impaired also had significantly higher BDI scores, although the mean scores were not in the depressed range. The percentage of patients with cirrhosis did not differ significantly between groups. There was also no significant difference between the cognitively impaired and not impaired groups in serum aspartate aminotransferase levels.

A logistic regression (Hosmer and Lemeshow, 1989) was performed with CRS, BDI, and Shipley IQ as predictors of impairment. BDI was not significant after adjustment for the other variables. Separate regressions using IQ and CRS showed that IQ was a better predictor than CRS, although each was highly significant (IQ Wald $\chi^2 = 33.89$, $p < .0001$; CRS Wald $\chi^2 = 19.75$, $p < .0001$). The logistic regression showed that CRS accounted for 15% of the variance in cognitive impairment, whereas IQ alone accounted for 28% of the variance. A C statistic was calculated, which represents the area under the ROC curve in the regression, and this value was significantly higher using the IQ compared with the CRS scores (0.78 *vs*. 0.70; $p < .0058$; DeLong et al., 1988).

The Shipley IQ score, however, is made up of two components, a vocabulary subtest score and an abstraction subtest score. The IQ score includes an abstraction component, which is actually a current cognitive performance measure of abstract reasoning rather than a measure of crystallized or static knowledge. That is presumably why the Stern et al. (1996) formula for CRS uses the vocabulary subtest *t* score in its calculation, as it is not based on a measure of current cognitive manipulation but rather on long-standing vocabulary knowledge. To further investigate whether the IQ predictions were confounded with cognitive performance rather than a simple proxy for CR, logistic regressions were performed on prediction of impairment using the vocabulary subtest *t* score alone and the abstraction subtest *t* score alone. As expected, the abstraction *t* score accounted for more of the variance (21%) than the vocabulary *t* score (17%), suggesting there is at least some confounding with other measures of cognitive performance. However, the C statistic was not significantly different between the two values ($p = .90$), and neither the verbal *t* score C statistic nor the abstraction *t* score C statistic were significantly different from the CRS C statistic ($p = .10$ and $p = .12$, respectively; data not shown).

When patients were classified as having a low CRS *versus* a high CRS, based on a median split, 43% of patients with a low CRS were classified as impaired, whereas 20% of patients with a high CRS were so classified (see Table 2). If patients were classified as having lower IQ *versus* higher IQ, based on the full Shipley test on the basis of a median split, 48% of the lower IQ patients would be classified as impaired *versus* 15% impaired in the higher IQ group. Further inspection of Table 2 reveals that the low CRS patients had individual test scores in the deficit range for verbal recall (SR), CVMT, and SDLT, tests reflecting verbal memory, nonverbal memory, and working memory. The high CRS patients also showed a deficient average verbal recall, whereas the average performance on CVMT and SDLT tests

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Table 1. Demographics and characteristics of cognitively impaired *versus* not impaired groups

Variable	Impaired[a] (n = 63) Mean or %	*SD*	Not impaired (n = 135) Mean or %	*SD*	p value
Cognitive Reserve Score[b]	241	112	331	125	<.0001
Cognitive Reserve Score (using full IQ score)	239	114	334	133	<.0001
Shipley IQ	91	12	104	11	<.0001
Shipley Vocabulary subtest *t* score	46	11	54	10	<.0001
Shipley Abstraction subtest *t* score	49	11	58	11	<.0001
Age	51	6	50	8	.75
Education level (0–22)	12.6	1.8	13.8	2.5	.0002
Occupation code (1–6)	3.7	1.5	4.2	1.6	.0402
% Female	30%		30%		.94
% Cirrhosis	40%		36%		.65
BDI-II Depression Score (0–63)	8.5	6.8	6.1	6.2	.0135
Serum AST (×ULN)	2.6	2.00	2.5	1.8	.54

Note. BDI-II = Beck Depression Inventory II; AST = aspartate aminotransferase; ULN, upper limit of normal.
[a]Impairment defined as a Global Deficit Score ≥ 1, determined from a battery of 10 standard neuropsychological test scores.
[b]Cognitive Reserve Score determined by relative ranking of occupational category, education, and Shipley Vocabulary subtest *t* score.

did not reach the cutoff for deficient performance (score of 1 or higher), even though they did show a tendency in this direction (score of 0.7).

DISCUSSION

The distribution of IQ scores in the HALT-C Trial population was similar to the distribution of IQ scores in the general U.S. population. Thus, the finding of cognitive impairment in 32% of the hepatitis C patient population in this study cannot be attributed to general intellectual abilities alone. Patients classified as cognitively impaired did have lower CRS, IQ, educational level, and occupational rating, but had similar severity of liver disease.

We have indicated that CR may be generally related to performance on neuropsychological tests in neurologically normal individuals, and reports of disease or treatment-specific interactions have already been described, includ-

Table 2. Neuropsychological test performance of hepatitis C patients with low *versus* high cognitive reserve

Variable	Low cognitive reserve (vocabulary *t* score) (n = 100) Mean	*SD*	High cognitive reserve (vocabulary *t* score) (n = 98) Mean	*SD*	p value
% Cognitive impairment[a]	43%		20%		.0006
Shipley Vocabulary *t* score	46	10	56	9	<.0001
Shipley Abstraction *t* score	51	11	60	10	<.0001
BDI-II Depression score	7.5	6.8	6.2	6.1	.18
Recall deficit score	2.7	1.9	1.7	1.8	.0001
CVMT deficit score	1.2	1.6	0.7	1.2	.0093
Digit span(f+b) deficit score	0.7	0.8	0.2	0.5	<.0001
Digit symbol deficit score	0.4	0.8	0.1	0.4	.0083
Serial digit learning deficit score	2.1	2.2	0.7	1.4	<.0001
Finger tapping(D+ND) deficit score	0.3	1.0	0.1	0.4	.0218
WCST deficit score	0.8	1.5	0.4	1.2	.0210
COWAT deficit score	0.1	0.3	0.0	0.2	.10
Trails A+B deficit score	0.7	1.4	0.4	1.0	.0362

Note. BDI-II = Beck Depression Inventory II; CVMT = Continuous Visual Memory Test; WCST = Wisconsin Card Sorting Test; COWAT = Controlled Oral Word Association Test.
[a]Cognitive impairment defined as Global Deficit Scores ≥ 1.

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ing the reports of Satz et al. (1993) and Stern et al. (1996) for patients with HIV. In addition, over a 1-year period, Basso and Bornstein (2000) found that HIV-infected men with above average IQ showed no declines on measures of executive function. However, those in HIV symptomatic groups with average IQ did show decline. No decline was evident in the asymptomatic group, whether IQ was above or below average. Therefore, it again appears that early cognitive impairments in patients with symptomatic HIV-1 infection are most evident in individuals with lower CR.

In the present study, as in the reports studying patients infected with HIV, patients with lower CRS appear to be more vulnerable to untoward cognitive effects in the presence of HCV infection. It may be that individuals with lower CR are less able to cognitively adapt to neurological or neurophysiological changes caused by infections. HCV-infected individuals with a higher CRS also appear to have levels of impairment that differ significantly from that reported in a nondiseased population by Axelrod and Wall (2003; 20% *vs*. 15%; $p = .0064$). It is quite possible that, even if patients with a higher CRS are less susceptible to the effects of HCV on cognition, a higher CRS is not entirely prophylactic.

The CRS used in this study was calculated according to the methods described by Stern et al. (1996), which included Shipley vocabulary subtest *t* scores, educational level, and occupational rating. In that study of patients infected with HIV, CRS was a significant predictor of the likelihood of cognitive impairment. Again, the CRS includes classifications for education and occupation and, in addition to providing consistency with the study by Stern et al. (1996), CRS adds functional considerations and appears to be a valid proxy for CR for inclusion in future studies. Although apparently accounting for more of the variance in cognitive test performance than the CRS, the Shipley IQ is likely confounded with cognitive measures due to the inclusion of abstract reasoning.

Patients infected with HCV appear to be at significantly increased risk for cognitive impairment in the presence of lower CR. This finding is similar to those in patients infected with HIV and underscores the importance of taking CR into consideration when conducting large-scale clinical trials. These more pronounced deficits in verbal recall, nonverbal recall, and working memory remain consistent with subcortical cognitive inefficiency as noted in Fontana et al. (2005). Whereas all three of these tests reached average deficit levels in the low CR group, the verbal recall test was the only test whose average value was in the deficient range in the high CR group, even though the other two tests tended in that direction.

Whereas lower CR is likely related to lower performance on cognitive tests independent of disease, there does appear to be a significant disease by CR interaction in this study, similar to that reported in other disease states. Again, severity of liver disease did not significantly differ between higher and lower CR groups, arguing against differential disease status impacting cognitive performance in the groups. There was an absence of significant correlation between lifetime substance use and psychiatric diagnoses as indicated in our earlier study (Fontana et al., 2005). Our findings speak to the importance of CR variables in the clinical manifestations and/or neuropathological consequences of infectious diseases.

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